--114. A resolved gutless adenovirus vector produced by the method of claim 113.

--115. An adenovirus library comprising a plurality of adenovirus vectors from claim 59, 76 or 98 expressing fiber proteins which are displayed and modified by random peptide insertions.

--116. The library of claim 115, wherein said fiber protein so displayed comprises a random peptide substituted in the G-H loop of the fiber protein knob domain.

--117. A screening method for targeting adenovirus vectors for gene therapy comprising contacting the adenovirus library of claim 115 with a plurality of cells so that the cells are transduced with the adenovirus vectors of the adenovirus library transduction occurs and detecting the cells so transduced.

--118. The adenovirus vector of claim 67, 68, 88, 89, 100, or 101 further comprising a nucleotide sequence encoding a rep78 protein.

--119. The adenovirus vector of claim 61, 86, and 102, wherein the inverted terminal repeat sequnences are from the same adenovirus serotype.

--120. The adenovirus of claim 100 or 101 further comprising an inverted repeat sequence located 3' to the left inverted terminal repeat sequence or located 5' to the right inverted terminal repeat sequence.

REMARKS

Claims 1-58 were pending but cancelled. New claims 59-120 were added. Accordingly, new claims 59-120 are being examined.

Support for new claims 59-120 maybe found in specification as originally filed and do not involve new matter. Entry of these changes is respectfully requested.

Support for claim 59 is found in originally filed claims 1 and 12.

Support for claim 60 is found in originally filed claim 2.

Support for claim 61 is found in the specification on page 23, lines 21-23.

Support for claim 62 is found in originally filed claim 7.

Support for claim 63 is found in originally filed claim 3.

Support for claim 64 is found in originally filed claim 4.

Support for claim 65 is found in originally filed claim 51.

Support for claim 66 is found in originally filed claim 52.

Support for claim 67 is found in originally filed claim 5.

Support for claim 68 is found in originally filed claim 6.

Support for claim 69 is found in originally filed claim 8.

Support for claim 70 is found in originally filed claim 9.

Support for claim 71 is found in originally filed claim 11.

Support for claim 72 is found in originally filed claim 12.

Support for claim 73 is found in originally filed claim 13.

Support for claim 74 is found in originally filed claim 14.

Support for claim 75 is found in originally filed claim 15.

Support for claim 76 is found in originally filed claims 16 and 12.

Support for claim 77 is found in originally filed claim 17.

Support for claim 78 is found in originally filed claim 18.

Support for claim 79 is found in originally filed claim 19.

Support for claim 80 is found in originally filed claim 20.

Support for claim 81 is found in originally filed claim 21.

Support for claim 82 is found in originally filed claim 22.

Support for claim 83 is found in originally filed claim 23.

Support for claim 84 is found in originally filed claim 24.

Support for claim 85 is found in originally filed claim 25.

Support for claim 86 is found in the specification page 23, lines 21-23.

Support for claim 87 is found in originally filed claims 27 and 7.

Support for claim 88 is found in originally filed claim 26.

Support for claim 89 is found in originally filed claim 27.

Support for claim 90 is found in originally filed claim 28.

Support for claim 91 is found in originally filed claim 29.

Support for claim 92 is found in originally filed claim 30.

Support for claim 93 is found in originally filed claim 31.

Support for claim 94 is found in originally filed claim 32.

Support for claim 95 is found in originally filed claim 33.

Support for claim 96 is found in originally filed claim 34.

Support for claim 97 is found in originally filed claim 35.

Support for claim 98 is found in originally filed claim 36 and 12.

Support for claim 99 is found in originally filed claim 37.

Support for claim 100 is found in originally filed claim 38.

Support for claim 101 is found in originally filed claim 39.

Support for claim 102 is found in the specification page 23, lines 21-23.

Support for claim 103 is found in originally filed claim 40.

Support for claim 104 is found in originally filed claim 41.

Support for claim 105 is found in originally filed claim 42.

Support for claim 106 is found in originally filed claim 43.

Support for claim 107 is found in originally filed claim 44.

Support for claim 108 is found in originally filed claim 46.

Support for claim 109 is found in originally filed claim 47.

Support for claim 110 is found in originally filed claim 50.

Support for claim 111 is found in originally filed claim 51.

Support for claim 112 is found in originally filed claim 52.

Support for claim 113 is found in originally filed claim 53.

Support for claim 114 is found in originally filed claim 54.

Support for claim 115 is found in originally filed claim 55.

Support for claim 116 is found in originally filed claim 59.

Support for claim 117 is found in originally filed claim 57.

Support for claim 118 is found in originally filed claim 58.

Support for claim 119 is found in the specifications page 17, lines 1-10.

Support for claim 120 is found in originally filed claim 45.

Novelty Rejection

In the Written Opinion, claims 3, 4, 12-14, 16-35, 45-47, 55-57 and 59 were found novel. However, claims 1, 2, 5-11, 15, 36-44, 48-54, and 58 were found allegedly anticipated by James Wilson et al. (U.S. Patent No. 5,856,152, issued January 5, 1999) (referred to hereafter as the Wilson patent).

Applicants respectfully disagree for the following reasons.

Applicants will discuss novelty as to the independent claims, i.e., claims 1, 36 and 53. To the extent that these claims are novel, then any claim dependent thereon must also be novel.

Applicants' Invention

Applicants claim novel first generation adenoviral vectors, gutless vectors and methods for producing gutless vectors.

In the subject application first generation adenoviral vectors are adenoviral vectors devoid several early replication genes (Specification at page 21, lines 24-29).

Gutless vectors of the invention are adenoviral vectors that are devoid of all adenoviral genes and therefore are unable to replicate in an infected host cell. (Specification at page 25, lines 21-22.)

Further, the invention provides methods for making gutless vectors by homologous recombination. Parental adenoviral vectors that contain homologous sequences infect a host cell. During replication the regions of overlapping homology direct homologous recombination resulting in a resolved recombinant gutless adenoviral vector. Regions of overlapping homology can flank a transgene or be within the transgene (specification at page 25 lines 9-27).

Wilson does not teach the invention of claim 1 (now claim 59)

Claim 1 (now claim 59) is direct to a first generation recombinant adenovirus vector comprising:

a) A left adenovirus inverted terminal repeat sequence;

b) An adenoviral packaging sequence 3' to the left adenovirus inverted terminal repeat sequence;

c) A first inverted repeat sequence 3' to the adenovirus packaging sequence;

d) A transgene cassette sequence 3' to the first inverted repeat sequence;

e) A second inverted repeat sequence as in (c) 3' to the transgene cassette;

f) At least one adenoviral sequence which directs adenoviral replication 3' to the right inverted repeat; and

g) A right adenoviral inverted terminal repeat sequence 3' to the adenoviral replication gene.

The Wilson patent describes a hybrid vector construct. The hybrid vector construct of the Wilson patent shares some similarity with the claimed construct. For example, the hybrid vector construct of the Wilson patent comprises a left adenovirus inverted terminal repeat sequence (claim 1(a) of the subject patent found on column 6, lines 1-55); an adenoviral packaging sequence (claim 1(b) of the subject patent found on column 6, lines 1-55); a transgene cassette sequence (claim 1(d) of the subject patent found on column 6, lines 1-55); at least one adenoviral sequence which directs adenoviral replication (claim 1(f) of the subject patent found on column 6, lines 1-55); and a right adenoviral inverted terminal repeat sequence (claim 1(g) of the subject patent found on column 6, lines 1-55).

In contrast to the claimed vector, the hybrid vector construct of the Wilson patent does not teach a first inverted repeat sequence 3' to the adenovirus packaging sequence

(claim 1(c) of the subject patent found on column 6, lines 1-55) or a second inverted repeat sequence 3' to the transgene cassette (claim 1(e) of the subject patent found on column 6, lines 1-55).

This difference is important because the hybrid vector of the Wilson patent functions requires the assistance of a co-infected helper vector within a cell in order to deliver the transgene cassette in the hybrid vector. Together the hybrid and helper vectors provide high titer transgene delivery to a host cell. Further, together they stably integrate the transgene into a host cell chromosome.

In contrast, the claimed vector comprises IR sequences that flank a transgene cassette that provides high titer transgene delivery to a host cell without the assistance of helper virus. Since the use of helper virus is generally regarded as unsafe in a subject, the claimed vector is an important tool for high titer transgene delivery to a host cell.

Because the Wilson patent did not teach an adenovirus vector with IR sequences flanking a transgene cassette, claim 1 (now claim 59) is novel with respect to the Wilson patent.

Wilson does not teach the invention of claim 36 (now claim 98)

Claim 36 (now claim 98) is directed to a gutless adenoviral vector. It comprises

a. A left adenovirus inverted terminal repeat sequence;
b. An adenoviral packaging sequence 3' to the left adenovirus inverted terminal repeat sequence;
c. A first inverted repeat sequence 3' to the adenoviral packaging sequence;
d. A transgene cassette sequence 3' to the first inverted repeat sequence;
e. A second inverted repeat sequence 3' to the transgene cassette;
f. A second adenoviral packaging sequence 3' to the second inverted repeat sequence; and

g. A right adenoviral inverted terminal repeat sequence 3' to the second adenoviral packaging,

wherein the left and right terminal repeat sequences permit integration of the transgene cassette sequence into the host cell genome.

Wilson did not teach a gutless vector, i.e., one that is devoid of all adenoviral gene having a transgene cassette flanked by IRs. However, even if the first generation vector of Wilson can be characterized as a gutless vector, as discussed above, the Wilson patent did not teach an adenovirus vector with IR sequences flanking a transgene cassette. Therefore, claim 36 (now claim 98) is novel with respect to the Wilson patent.

Wilson does not teach the invention of claim 53 (now claim 113)

Claim 53 (now claim 113) is directed to a method of producing a resolved gutless recombinant Ad vector by homologous recombination in a suitable cell. The method involves using two parental recombinant Ad vectors each comprising a transgene cassette containing a portion of a selected transgene with a region of overlapping homology. In the method the two parental recombinant Ad vectors are contacted with each other so that the first and second parental recombinant Ad vectors undergo homologous recombination at the region of overlapping homology. This results in a resolved recombinant gutless Ad vector having both portions of the selected transgene that is flanked by a pair of ITRs.

Wilson teaches a method to produce a recombinant adeno-associated virus that requires 5' and 3' cis-elements necessary for replication and encapsidation provided by a helper adenovirus. (Wilson patent column 14 lines 41-47)

Wilson did not teach gutless vectors let alone methods of producing a resolved gutless recombinant Ad vector by homologous recombination in a suitable cell. Therefore, claim 53 (now claim 98) is novel with respect to the Wilson patent.

Lack of Inventive Step Rejection

In the Written Opinion, the Examiner took the position that claims 1-58 lacked inventive step in light of the combination of the Wilson patent, PCT application WO98/54346 (referred herein as Genvec or Genvec application), and WO97/38723 (referred herein as Immusol or Immunsol application).

Applicants will discuss lack of inventive step as to the independent claims, i.e., claims 1, 36 and 53. To the extent that these claims lack inventive step, then any claim dependent thereon must also lack inventive step.

The combination of the Wilson patent, Genvec application, and Immunsol application is not suggestive of the first generation adenoviral vector of claim 1 (now claim 59)

Claim 1 (now claim 59) has been discussed above. The Wilson patent has been described above. Contrary to the claimed vector, the Wilson patent does not teach an adenovirus vector with IR sequences flanking a transgene cassette.

None of the remaining cited references cure this deficiency.

The GENVEC application describes an adenovirus vector with a modified fiber protein. The invention provides a trimer comprising three monomers each having an amino terminus of an adenoviral fiber protein and each having a trimerization domain. The trimer exhibits reduced affinity for a native substrate compared to a native adenoviral fiber trimer. (Specification at page 7, lines 28-38.)

The GENVEC application does not describe an adenovirus vector comprising IR sequences flanking a transgene cassette. This missing component is important because it allows the vector to undergo homologous recombination and/or direct transgene integration. The adenoviral vector of the prior art requires a modified capsid

protein to target the adenoviral vector and alters the native pathway by which this vector of the prior art infect host cells. (Genvec at page 7, lines 28-38).

The IMMUSOL application describes viral vectors that are targeted to selected cell types by blocking the wild-type viral cell binding site and incorporating a targeting agent into the vector particle. The targeting agent binds to the selected cell type by binding a molecule on the cell surface or the cell, or by binding a second targeting agent which binds to the selected cell. (Specification at page 17, lines 12-22.)

The IMMUSOL application does not teach or suggest an adenovirus vector comprising IR sequences that flank a transgene cassette.

The combination cannot suggest the claimed invention since none of the cited references teach an adenovirus vector comprising IR sequences that flank a transgene cassette.

The combination of the Wilson patent, Genvec application, and Immunsol application is not suggestive of claim 36 (now claim 98)

Claim 36 (now claim 98) has been discussed above. Contrary to the claimed vector, Wilson did not teach a gutless vector or any vector with IR sequences flanking a transgene cassette.

None of the remaining cited references cure this deficiency.

Neither the Genvec or Immusol application describe an adenovirus vector comprising IR sequences that flank a transgene cassette.

The combination cannot suggest the claimed invention since none of the cited references teach an adenovirus vector comprising IR sequences that flank a transgene cassette.

The combination of the Wilson patent, Genvec application, and Immunsol application is not suggestive of claim 53 (now claim 113)

Claim 53 (now claim 113) has been discussed above. Contrary to the claimed method, Wilson did not teach gutless vectors let alone methods of producing a resolved gutless recombinant Ad vector by homologous recombination in a suitable cell.

None of the remaining cited references cure this deficiency.

The Genvec application does not teach a method to produce a recombinat gutless adenoiral vector. The Genvec application teaches methods for propogating an adenovirus with a modified capsid in a cell line with a non-natural cell surface receptor; purifying adenovirus that a have specific ligand on their capsid; and inactivating in a fluid an adenovirus having a ligand recognizing a fluid-bourne substrate. The Immusol application teaches a method of selecting a targeted adenoviral vector, it does not teach a method to produce a recombinant gutless adenoviral vector.

The combination fails to suggest the claimed invention since none of the cited references teach an adenoviral vector with IRs or sequences with overlapping homology. These elements are required to produce the adenovirus vector with a transgene flanked by IRs by homologous recombination.

Conclusion

Applicants submit that new claims 59-120 satisfy the requirements of PCT Art. 33 for novelty since the Wilson patent failed to teach an adenovirus vector comprising IR sequences that flank a transgene cassette. Further, new claims 59-120 satisfy the requirements of PCT Art. 33 for inventive since none of the cited Wilson patent, Genvec application and Immusol application teaches or suggests an adenovirus vector

comprising IR sequences that flank a transgene cassette or methods of producing them.

No fee is deemed necessary in connection with the filing of this response. If any fee is necessary, the Patent Office is authorized to charge any additional fee to Deposit Account No. 50-0306.

Respectfully submitted,

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